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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/704,054	D'AMATO, ROBERT	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,25-31 and 33-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,25-31 and 33-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 July 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 23, 25-31 & 33-71 ARE PRESENTED FOR EXAMINATION

Continued Examination Under 37 CFR § 1.114

A request for continued examination under 37 CFR § 1.114, including the fee set forth in 37 CFR § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR § 1.114, and the fee set forth in 37 CFR § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR § 1.114. Applicant's submission filed on 7/12/2007 has been entered. Accordingly, claims 23, 41 and 49 have been amended.

Priority

This instant application is a division of U.S. Non-Provisional Application No. 09/545,139, filed 4/7/2000, now U.S. Patent No. 6,469,045, issued 10/22/2002, which is a division of U.S. Non-Provisional Application No. 08/950,673, filed 10/16/1997, now U.S. Patent No. 6,071,948, issued 6/6/2000, which is a continuation of U.S. Non-Provisional Application No. 08/468,792, filed 6/6/1995, now U.S. Patent No. 5,712,291, issued 1/27/1998, which is a continuation of U.S. Non-Provisional Application No. 08/168,817, filed 12/15/1993, now U.S. Patent No. 5,629,327, issued 5/13/1997, which is a continuation-in-part of U.S. Non-Provisional Application No. 08/025,046, filed 3/1/1993, now abandoned.

Support for the instant claims was found in U.S. Non-Provisional Application No. 08/025,046, filed 3/1/1993. As such, the earliest effective U.S. filing date afforded the instant claims has been determined to be March 1, 1993.

Drawings

The drawings were received on 7/12/2007. These drawings are sufficient to overcome the objection to the drawings set forth in the Office Action mailed 5/10/2007. Accordingly, the objection to the drawings is hereby *withdrawn*.

Response to Arguments

Applicant's arguments traversing the rejection of claims 23, 25-31 and 33-71 under 35 U.S.C. § 112, 1st Paragraph (Enablement) have been fully considered but they fail to persuade the Examiner of an error in his determination that the presently claimed invention is not enabled by the disclosure.

Applicant submits that the pending claims comply with the enablement requirement of 35 U.S.C. § 112, 1st Paragraph because the specification provides a "reasonable amount of guidance" to practice the claimed invention. In support of this argument, Applicant directs the Examiner's attention to various points in the specification where modes of administration (page 20, lines 22-34), doses of thalidomide (page 21, lines 1-10) and dosage forms and formulations (page 21, lines 24 to page 23, lines 23) are disclosed. Firstly, the Examiner would like to clarify the record with respect to his statement in the previous Office Action that the formulations and administration routes taught in the specification are traditionally used for all therapeutic agents, regardless of the condition to be treated or agent to be administered. This observation was directed, not to lack of specificity with regard to administering thalidomide, but to the lack of specificity with regard to the treatment of tumors with thalidomide. The specification contemplates the treatment of any and all diseases "mediated by undesired and uncontrolled

angiogenesis" (page 8, lines 18-22). Thus, the administration routes, doses and dosage forms and formulations are **not** limited to the treatment of tumors, but to the treatment of any and all diseases mediated by uncontrolled angiogenesis. Further, the specification is **not** limited to the treatment of such diseases with *only* thalidomide. For example, other compounds are disclosed at pages 12-20 of the specification, all of which are said to be useful compounds for inhibiting angiogenesis and are thus useful in treating any and all diseases mediated by uncontrolled angiogenesis. Thus, Applicant's argument that the specification provides a "reasonable amount of guidance" to practice the claimed invention is not persuasive because the guidance provided in the specification is not in any way reasonably specific to the treatment of tumors with thalidomide.

Next, Applicant argues that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, the enablement requirement is satisfied (emphasis in original). The basis of this argument appears to be that since thalidomide inhibits angiogenesis and angiogenesis is correlated to tumor growth, the specification necessarily discloses a method of making and using the invention that correlates to the entire scope of the claims. Firstly, as Applicant correctly states, the Examiner recognizes the correlation between tumor growth and angiogenesis (pages 3 and 5 of the previous Office Action). However, the fact that a particular compound inhibits angiogenesis in a model of angiogenesis does not, *a priori*, mean that said compound necessarily inhibits the formation (*i.e.*, prevents a tumor from forming), growth and/or metastases of tumors as instantly claimed. In fact, the Examiner has provided substantial prior art evidence that thalidomide is **not effective** in treating cancer or inhibiting tumor growth. Applicant appears to

have interpreted this reasoning by the Examiner to mean that he is confusing the requirements under law for obtaining a patent with the requirements for obtaining government approval for marketing a particular drug for human consumption (page 10 of arguments). However, this is not the case – the Examiner is well aware of the differences between the two requirements. The Examiner is simply providing evidence that the claimed invention, if not entirely ineffective, is not at all predictable. Applicant is reminded that the unpredictability of the art is one factor to be considered in establishing lack of enablement under 35 U.S.C. § 112, 1st Paragraph (*In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404). Secondly, it was well known in the art prior to Applicant's invention that angiogenesis is involved in tumor growth. Further, as evidenced by the prior art cited by the Applicant and the Examiner, thalidomide had been administered to both animals and humans for the treatment of cancer and tumors well before Applicant's invention (see Grabstald *et al.*, 1965; Olsen *et al.*, 1965; Roe *et al.*, 1963; Bach *et al.*, 1963; DiPaolo *et al.*, 1964; and DiPaolo *et al.*, 1963). In fact, were it not for the entirely unpredictable nature of the claimed invention, the present claims would be clearly obvious in view of the prior art. However, because such administration of thalidomide to humans and animals was shown to <u>not</u> be effective, the art cannot be said to render obvious the claimed invention because there would simply be no reasonable predictability or expectation of success.

With respect to Applicant's arguments that the specification "clearly describes that inhibition of angiogenesis with thalidomide would lead to the inhibition of tumor growth or metastasis", while this prophetic disclosure is scientifically reasonable, the prior art clearly discourages this hypothesis. Applicant further argues that the Examiner has not provided any evidence that the animal models of angiogenesis disclosed in the specification do not correlate

with the inhibition of tumors. This is simply not the case. The Examiner has cited numerous articles that teach that administration of thalidomide did not inhibit tumor growth (*e.g.*, Bach *et al.*, 1963; DiPaolo *et al.*, 1964; and DiPaolo *et al.*, 1963; Gutman *et al.*, 1996). Thus, the animal models disclosed in the specification clearly and unequivocally do not correlate to the inhibition of tumor growth.

Applicant next argues that the prior art as a whole supports the use of thalidomide for inhibiting tumors, based on the discovery of the present inventor that thalidomide inhibits angiogenesis. However, well prior to Applicant's discovery of this mechanism of thalidomide action, the prior art attempted to use thalidomide to treat cancer and inhibit tumor growth. In fact, it was well established in the prior art that thalidomide was **not effective** at inhibiting tumor growth and skilled artisans in the field gave up trying to develop thalidomide for this purpose (see Grabstald *et al.*, 1965; Olsen *et al.*, 1965; Roe *et al.*, 1963; Bach *et al.*, 1963; DiPaolo *et al.*, 1964; and DiPaolo *et al.*, 1963). Again, the prior art would be anticipatory, or at least render obvious the claimed invention, if administration of thalidomide to inhibit tumor growth or treat cancer actually worked. The fact remains that the claimed methods are entirely unpredictable and will likely not work for even a reasonable number of tumors, despite the guidance and direction Applicant provides in the specification.

Finally, Applicant argues that the *in vitro* or *in vivo* animal model examples in the specification, in effect, constitute working examples, as the examples correlate with a claimed method invention. However, as discussed *supra*, while the examples demonstrate that thalidomide inhibits angiogenesis, they do not correlate to inhibiting the formation, growth or metastasis of tumors. Applicant notes that human working examples are not required under 35 §

U.S.C. 1st Paragraph. The Examiner respectfully submits that he has never asked for nor required Applicant to provide human working examples. While it is true that a physician can determine whether thalidomide is effective in treating a tumor or inhibiting its metastasis, the determination in the present case is not routine. For example, using the prior art as guidance, the physician would not reasonably expect that thalidomide would be effective at inhibiting tumor growth, given that administration of thalidomide (in doses as instantly claimed) to 71 human patients having various cancers was not effective (Grabstald *et al.*, 1965). The skilled artisan might look to use animal models of tumor growth to determine which tumors are "sensitive to thalidomide" as instantly claimed. However, there are two main problems with this experimentation. First, animal tumor models rarely correlate to the treatment of a human disease, especially the treatment of cancer (see Sausville *et al.*, Cancer Research, 2006, vol. 66, pages 3351-3354 and Johnson *et al.*, British J. of Cancer, 2001, 84(10):1424-1431) (cited for evidentiary purposes). Second, animal models of tumor growth have been used in the prior art to test the efficacy of thalidomide and thalidomide was shown to not be effective in inhibiting tumor growth. Thus, if inhibition of angiogenesis correlates to inhibition of tumor growth and metastases as Applicant asserts, then there must be something inherently flawed with the known animal models of tumor growth.

In view of the above discussion, it is apparent that the skilled artisan would have to engage in undue experimentation to practice the full scope of the claimed invention with no reasonable expectation of success. The rejection of claims 23, 25-31 and 33-71 under 35 U.S.C. 112, 1st Paragraph is maintained for the reasons of record and reiterated below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23, 25-26, 30-31, 33-35, 39-43, 47-52 and 56-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23, 41 and 49 recite the administration of "an effective amount" of thalidomide. This limitation is indefinite because it is not clear what the amount being administered is effective for. The preamble of the claim is not linked to the body of the claim in such a way as to clearly convey that the "effective amount" being administered is effective to treat the condition recited in the preamble. The phrase "an effective amount" has been held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. *In re Fredericksen* 213 F.2d 547, 102 USPQ 35 (CCPA 1954). In the instant case, an effective amount of thalidomide could be interpreted to be an amount that inhibits angiogenesis but does not necessarily inhibit the formation of tumors, growth of tumors and/or the metastasis of tumors. Claims dependent from claims 23, 41 and 49 are included in this rejected, except for those claims that recite specific dose ranges.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 25-31 and 33-71 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) The breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to inhibiting the formation (*i.e.*, prevention), growth or metastasis of tumors sensitive to angiogenesis in humans comprising the administration of thalidomide.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art.

It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art with respect to animal models of cancer, the examiner cites Sausville *et al.* (Cancer Research, 2006, vol. 66, pages 3351-3354) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Sausville *et al.*, cited for evidentiary purposes, teaches that traditionally explored tumor model systems are insufficient to predict how actual human beings will respond to treatment in the clinic (page 3351, left column). Even when drugs with evidence of anticancer activity in preclinical *in vivo* models are given their maximum tolerated dose in humans, they frequently fail to produce useful activity in humans (*id.*). Also, with regard to unpredictability, Johnson *et*

al., also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

As illustrative of the state of the art with respect to administering thalidomide to inhibit tumor growth, the examiner cites Bach *et al.* (Acta Path., 1963, *59*:491-499) (cited by applicant), Gutman *et al.* (Anticancer Research, 1996, *16*:3673-3677), DiPaolo (Cancer Chemotherapy Reports, 1963, *29*:99-102) (cited by applicant), Thomas *et al.* (Current Opinion in Oncology, 2000, *12*:564-573) and Grabstald *et al.* (Clinical Pharmacology and Therapeutics, 1965, *6*:298-302) (cited by applicant). All references are cited for evidentiary purposes only.

Bach *et al.* studied the possible antineoplastic effect of thalidomide in experimental mouse models. The reference also discusses a report in which a woman with an X-ray resistant pelvic tumors was treated with thalidomide (400 mg daily). The tumors increased in size during the treatment. Bach *et al.* transplanted NJA tumors (a transplantable leukemia) and PBH tumors (an adenocarcinoma) in mice (page 494). The mice were then treated with varying doses (11.2, 112.0, 560.0 and 1120.0 mg/kg) of thalidomide (page 495). In mice with PBH tumors, all thalidomide treated mice died before controls (pages 496-497). In the NJA implanted mice, there was no significant effect of thalidomide on the survival times of the animals. Further, histological exam revealed no difference with regard to the extent of the leukemic infiltrations in the organs between treated and untreated mice (pages 496-497). The authors conclude that thalidomide had no antineoplastic effect (page 498).

Gutman *et al.* tested the efficacy of thalidomide in treating solid tumors in mice (Abstract). B16-F10 (melanoma) and CT-26 (colon carcinoma) cells were injected in mice and the mice then received 0.3-1.0 mg thalidomide (*id.*). There was no growth retardation in CT-26 bearing mice or in mice with pulmonary or peritoneal metastases of B16-F10 melanoma (*id.*). All tumors reached maximum size, similar to controls. Further, morphological exam revealed that in both thalidomide and control groups, all mice had developed an intact network of new blood vessels (*id.*). In conclusion, the authors report that the present study did not demonstrate a sustained, reproducible, anti-angiogenic effect of thalidomide in solid tumors growing in mice (page 3676).

DiPaolo also studied the effects of thalidomide in treating standard rat and mouse tumors, including adenocarcinoma, Ehrlich ascites, leukemia, sarcoma, Murphy-Sturm, lymphosarcoma and Walker 256 (Table 1). The daily dose of thalidomide was 500 mg/kg (*id.*). Based on the results of this study, DiPaolo concludes, "thalidomide is ineffective against transplantable cancers" (page 102).

Thus, in three separate studies, thalidomide was ineffective in inhibiting tumor growth in mouse models of cancer. Given this information, the skilled artisan would not reasonably expect thalidomide to be effective in treating tumors in humans.

Grabstald *et al.* is cited as evidence to support the unpredictability of treating tumors in humans using thalidomide. In fact, Applicant admits that Grabstald *et al.* teach away from the present invention (see Response filed January 27, 2005). The reference teaches that thalidomide was administered to 71 patients with a wide spectrum of cancers (Abstract). There was no evidence of an objective response in any cancer except one patient with renal cell cancer (*id.* at

page 301). The authors conclude, "further random trials of this [thalidomide] drug against cancer in man are not indicated" (page 301). It is noted that Grabstald *et al.* would clearly render obvious the claimed invention if the reference provided some reasonable predictability or expectation of success.

Thomas *et al.* provides a review of the current role of thalidomide in cancer treatment. Although the article will not be discussed in detail, several points are pertinent to the present rejection. Firstly, the article states that the first oncology studies of thalidomide were reported in 1965 (Grabstald *et al.*, cited *supra*). Further, another study of 21 patients with various solid tumors who were treated with thalidomide revealed no tumor regressions (page 564). Secondly, several clinical trials of thalidomide have been carried out (pages 566-569). Thalidomide has shown moderate effects in some cancers (gliomas – 2/36 patients had partial response, 2/36 patients had a minor response, and 12/36 had stable disease; Kaposi's sarcoma – 6/17 patients had a partial response, 8/17 patients withdrew from toxicity; renal cell carcinoma – 3/18 patients had partial response) (pages 566-567). However, there were no objective tumor responses in 63 patients with metastatic prostate cancer, no objective responses in 17 patients with melanoma, no objective responses in 12 patients with breast cancer or 19 patients with ovarian carcinoma, and no objective tumor responses in 17 patients with metastatic squamous cell carcinoma of the head and neck (in fact, 94% of patients had progressive disease) (pages 567-568). Thirdly, a summary of FDA new drug applications issued for thalidomide between 1997 and 1998 yielded data on 480 patients treated for breast, CNS, prostate, skin, colon, pancreas and kidney malignancies. Thalidomide was given in doses up to 2400 mg daily. Responses were observed in 36 patients (7.5%), 10 of who had received combination therapy (*i.e.* not thalidomide alone), whereas 53%

of patients discontinued therapy because of toxicity (page 568). Thus, it is clear that the treatment of tumors in humans with thalidomide is extremely unpredictable and in the majority of cases completely ineffective:

Applicants own admissions on the record provide further evidence that the treatment of tumors in humans with thalidomide is entirely unpredictable. For example, in Applicant's response filed 8/7/2006, applicant submitted that 19 references "indicate that thalidomide was not successful in inhibiting tumors in animals and humans" (page 16 of response filed 8/7/2006). Further, Applicant states (emphasis added), "Moreover, Applicant respectfully points out that several references actually teach that **thalidomide has cancer-promoting or carcinogenic activity**" (*id.*). Further still, Applicant states (emphasis added), "The references disclose **not only failure** but the **complete opposite effect** to the claimed invention" (*id.*). Applicant goes on to cite several studies wherein thalidomide was administered to humans with various tumors. Applicant concludes (emphasis added), "Again, **all of these studies failed to provide any promise for thalidomide as effective in inhibiting the formation or growth of tumors in humans**. The studies neither provide with any suggestion, **nor a reasonable expectation of success in inhibiting tumors in humans**" (*id.* at page 17). Thus, it is clear that thalidomide may actually promote cancer in some instances and in fact may have the opposite effect to that instantly claimed.

Thus, a preponderance of evidence suggests that treating tumors with thalidomide, particularly in humans, is extremely unpredictable and in most cases ineffective. Further, it is evident that thalidomide may actually have the complete opposite effect than those instantly.

2. The breadth of the claims

The claims vary in breadth; some (such as claim 23) vary broadly, reciting the prevention or inhibition of growth of any and all tumors sensitive to thalidomide (both benign and cancerous) by administering thalidomide. Conspicuously absent from the disclosure, however, is any indication exactly which human tumors are sensitive to thalidomide. As evidenced by the references cited *supra*, most human cancers and tumors are **not** sensitive to thalidomide treatment. Others, such as claim 34, are narrower, reciting specific tumors. All, however, are extremely broad insofar as they disclose the general prevention, growth inhibition and inhibition of metastases of tumors with thalidomide.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat all of the various tumors claimed, particularly in humans. The working examples are limited to demonstrating the anti-angiogenic activity of thalidomide in animal models of angiogenesis. While angiogenesis is one factor involved in tumor growth, there are many other factors that influence tumor growth. As such, the fact that thalidomide inhibits angiogenesis does not reasonably suggest that it will be effective in inhibiting tumor growth. In fact, as discussed *supra*, the prior art supports the idea that thalidomide is ineffective in inhibiting tumor growth in humans and therefore supports the Examiner's position that the working examples do not correlate to inhibition of tumor growth, let alone prevention of tumors or inhibition of tumor

metastasis. Thus, the Applicant at best has provided specific direction or guidance only for the inhibition of angiogenesis with thalidomide. Although broad doses and administration routes of thalidomide are described in the specification, these doses and administration routes are contemplated to be useful for the treatment of any all angiogenic-related conditions. No reasonably specific guidance is provided concerning useful therapeutic protocols for any specific conditions or diseases, particularly the treatment of tumors.

Further, there are no *in vitro* or *in vivo* experimental models of any diseases described, including cell proliferation or animal tumor models. While the administration routes disclosed in the specification are standard routes of administration for therapeutic agents, Applicant has provided no specific administration regimens (*e.g.* timing, specific doses, etc.) necessary to prevent, inhibit the growth of or inhibit metastases of any specific tumors. Finally, while Applicant recites a broad dose range (0.1 to 300 mg/kg/day), this dose range is not reasonably specific enough so as to provide adequate guidance to the skilled artisan in the treatment of tumors, especially considering that doses within this range have previously been administered to inhibit tumor growth or treat cancer and were entirely ineffective.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that thalidomide could be predictably used to prevent all tumors, inhibit the growth of all tumors and/or inhibit the metastasis of all tumors sensitive to thalidomide as inferred in the claims and contemplated by the specification. A preponderance of the evidence

suggests that thalidomide is ineffective in treating tumors in humans. Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

U.S. Non-Provisional Application No. 11/096,155

Claims 23, 25-29, 31, 33-40, 58-62, 67-68 and 71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-46 of copending Application No. 11/096,155. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and the claims of the '155 application recite the treatment of tumors comprising administering thalidomide. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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July 26, 2007

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